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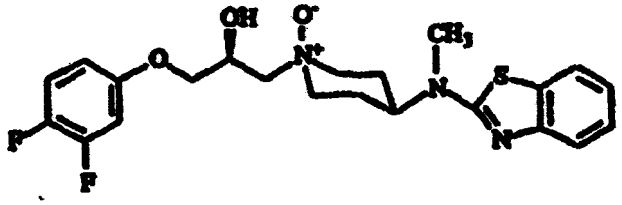
(54) Title: LUBELUZOLE N-OXIDE

(57) Abstract

The present invention is concerned with lubeluzole N-oxide(s), compositions containing the N-oxide(s), methods of preparing these and their use as a medicine, in particular in the treatment of conditions involving cerebral hypoxia.



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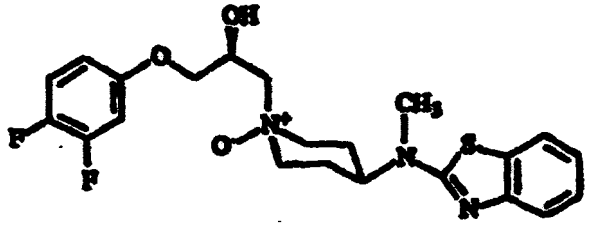

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LUBELUZOLE N-OXIDE

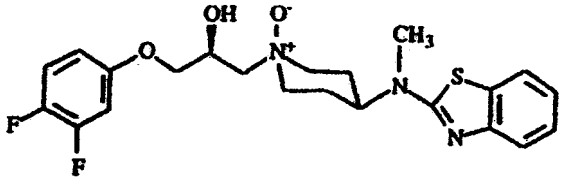
The present invention is concerned with neuroprotectant N-oxide forms of lubeluzole, compositions containing such N-oxide(s), methods of preparing these and their use as a medicine, in particular in the treatment of conditions involving cerebral hypoxia.

In US-4,861,785 there are described benzoxazol- and benzothiazolamine derivatives having anti-hypoxic and anti-anoxic activity. In WO-92/14,731 some of these benzothiazolamine derivatives were disclosed having useful anti-stroke activity. Injectable formulations of (S)-4-[(2-benzothiazolyl) methylamino]-α-[(3,4-difluoro-phenoxy)methyl]-1-piperidine-ethanol (generically known as lubeluzole) are disclosed in European Patent application No. 94203422.4 filed 24 November 1994.

Conditions involving cerebral hypoxia comprise stroke, more in particular ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage, and head trauma. The treatment of conditions involving cerebral hypoxia currently consists mainly of neuroprotective and of haematologic therapeutic strategies. Optimal therapies remain to be determined. Such an optimized therapy for the treatment of hypoxia is the subject of the present invention. In particular, it concerns providing an N-oxide of lubeluzole, a pharmaceutically acceptable acid addition salt form, a solvate or a stereochemically isomeric form thereof, as a new medicine for the treatment of conditions involving cerebral hypoxia. The product is suitable for intravenous and intradermal administration by infusion which is the most appropriate route of administration for hypoxic patients, and also orally, which route is most suitable for maintenace therapy. Experiments with the cis N-oxide form of lubeluzole in an animal model test of acute stroke indicate that it has superior neuroprotectant activity over the compound lubeluzole.

The N-oxides of lubeluzole are meant to comprise those compounds wherein one or more of the nitrogen atoms are oxidized, in particular those wherein the piperidine nitrogen is oxidized.

More in particular, the present invention is concerned with lubeluzole N-oxide, the cis and trans forms of which are represented by the following formulae :



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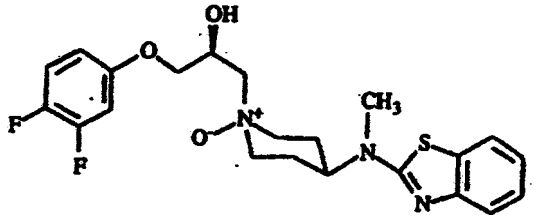

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Pharmaceutically acceptable acid addition salts comprise the therapeutically active, non-toxic salt forms obtained by treating a base form with an acid such as, for example, an inorganic acid, e.g. hydrochloric, hydrobromic, sulfuric, nitric, phosphoric acid ; or an organic acid, e.g. acetic, propanoic, hydroxyacetic, lactic, pyruvic, malonic, succinic, maleic, fumaric, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic acid. Solvates of lubeluzole N-oxide are, for example hydrates, alcoholates.

The cis-oriented N-oxide of lubeluzole is particularly preferred, and the most preferred form thereof is the hemihydrate, i.e. (-)-[cis] lubeluzole N-oxide hemihydrate.

The N-oxide(s) of lubeluzole can be prepared following art-known procedures of preparing oxides of nitrogen-containing products. They are conveniently prepared by dissolving lubeluzole in a solvent and adding thereto a sufficient amount of a suitable oxidant. Examples of such oxidants are hydrogen peroxide, peroxic acids, e.g. *m*-chloroperbenzoic acid, metal oxides, e.g. $NaWO_4$ and the like. Suitable solvents are, for example, water and halogenated hydrocarbons, in particular dichloromethane.

Hereinafter, the amounts of each of the ingredients in liquid compositions are expressed as percentages by weight based on the total volume of the formulation, unless otherwise indicated. Amounts in solid preparations are expressed as percentages by weight based on the total weight of the formulation, unless otherwise indicated.

Pharmaceutical compositions of lubeluzole N-oxide suitable as medicaments according to the present invention comprise a pharmaceutically effective amount of active ingredient and one or more pharmaceutically acceptable excipients or carriers as known in the art. The pharmaceutical compositions are adapted for oral or parenteral

(including intramuscular, subcutaneous, intradermal and intravenous) administration. The formulations are most conveniently presented in discrete dosage units. Generally, the pharmaceutically acceptable carrier for formulating the neuroprotectant lubeluzole N-oxide as an infusion is an aqueous solution (a) comprising water ; an isotonizing agent ; and acid, base or buffer substances sufficient to adjust the pH of the solution in the range of from 2.5 to 3.6.

In particular, the concentration of lubeluzole N-oxide in the present solutions (a) may range from 0.005% to 5%, preferably from 0.01% to 1%, more preferably from 0.02% to 0.2% and in particular is about 0.05%.

Further, the present solutions (a) conveniently comprise from 1 to 10% isotonizing agent. The use of glucose as isotonizing agent has the advantage that very clear solutions are obtained. Preferably, glucose is used in a concentration from 2 to 10%, most preferably of about 5%.

The solutions (a) further comprise acid and base substances to maintain the pH of the solution in the range from 2.5 to 3.6, preferably in the range from 3.0 to 3.4, most preferably at about 3.2. Preferably, the pH of the solutions (a) is adjusted by appropriate amounts of hydrochloric acid and sodium hydroxide. The pH may also be adjusted by buffer systems comprising mixtures of appropriate amounts of an acid such as phosphoric, tartaric or citric acid, and a base, in particular sodium hydroxide.

In order to increase the solubility of lubeluzole N-oxide in the present formulations, a solubilizer may be used. Conveniently, a cyclodextrin (CD) or a derivative thereof may be used. Appropriate cyclodextrin derivatives are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-cyclodextrin; hydroxy-C_{1-6}alkyl, particularly hydroxyethyl, hydroxypropyl or hydroxy-butyl; carboxy-C_{1-6}alkyl, particularly carboxymethyl or carboxyethyl; C_{1-6}alkyl-carbonyl, particularly acetyl; C_{1-6}alkyloxycarbonylC_{1-6}alkyl or carboxyC_{1-6}alkyloxy-C_{1-6}alkyl, particularly carboxymethoxypropyl or carboxyethoxy-propyl; C_{1-6}alkyl-carbonyloxyC_{1-6}alkyl, particularly 2-acetyloxypropyl. Especially noteworthy as solubilizers are β-CD, 2,6-dimethyl-β-CD, randomly methylated β-cyclo-dextrin, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD.

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl.

The average molar substitution (M.S.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The M.S.value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. In the cyclodextrin hydroxyalkyl derivatives for use in the compositions according to the present invention the M.S. as determined by mass spectrometry is in the range of 0.125 to 10, in particular of 0.3 to 3, or from 0.3 to 1.5. Preferably the M.S. ranges from about 0.3 to about 0.8, in particular from about 0.35 to about 0.5 and most particularly is about 0.4. M.S. values determined by NMR or IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

The average substitution degree (D.S.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The D.S. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. In the cyclodextrin derivatives for use in the compositions according to the present invention the D.S. as determined by MS is in the range of 0.125 to 3, in particular of 0.2 to 2 or from 0.2 to 1.5. Preferably the D.S. ranges from about 0.2 to about 0.7, in particular from about 0.35 to about 0.5 and most particularly is about 0.4. D.S. values determined by NMR or IR preferably range from 0.3 to 1, in particular from 0.55 to 0.75.

More particular β– and γ-cyclodextrin hydroxyalkyl derivatives for use in the compositions according to the present invention are partially substituted cyclodextrin derivatives wherein the average degree of alkylation at hydroxyl groups of different positions of the anhydroglucose units is about 0% to 20% for the 3 position, 2% to 70% for the 2 position and about 5% to 90% for the 6 position. Preferably the amount of unsubstituted β- or γ-cyclodextrin is less than 5% of the total cyclodextrin content and in particular is less than 1.5%. Another particularly interesting cyclodextrin derivative is randomly methylated β-cyclodextrin.

Most preferred cyclodextrin derivatives for use in the present invention are those partially substituted β-cyclodextrin ethers or mixed ethers having hydroxypropyl, hydroxyethyl and in particular 2-hydroxypropyl and/or 2-(1-hydroxypropyl) substituents.

The most preferred cyclodextrin derivative for use in the compositions of the present invention is hydroxypropyl-β-cyclodextrin having a M.S. in the range of from 0.35 to 0.50 and containing less than 1.5% unsubstituted β-cyclodextrin. M.S. values determined by NMR or IR preferably range from 0.55 to 0.75.

In order to minimize the risk of adverse reactions, an intravenous (or intradermal) formulation preferably contains as few ingredients as possible. Therefore, a formulation without a solubilizer such as a cyclodextrin is preferred. Further, the neuroprotectant solution (a) preferably does not contain a preservative. Oral liquid formulations on the other hand can comprise both a solubilizer such as a cyclodextrin and one or more preservatives.

In particular, the present invention relates to neuroprotectant solutions (a) comprising:
(i) 0.005 to 5% lubeluzole N-oxide or a pharmaceutically acceptable addition salt or a solvate thereof;
(ii) 1 to 10% isotonizing agent;
(iii) acid and/or base substances to adjust the pH in the range from 2.5 to 3.6 ; and
(iv) water q.s. ad 100%.

Preferably, the invention relates to neuroprotectant solutions (a) comprising:
(i) 0.01 to 1% lubeluzole N-oxide or a pharmaceutically acceptable addition salt or a solvate thereof;
(ii) 2 to 10% glucose;
(iii) hydrochloric acid and sodium hydroxide to adjust the pH in the range from 3.0 to 3.4 ; and
(iv) water q.s. ad 100%.

Most preferably, the invention relates to neuroprotectant solutions (a) containing approximately :
(i) 0.05% lubeluzole N-oxide or a pharmaceutically acceptable addition salt or a solvate thereof;
(ii) 5% glucose;
(iii) hydrochloric acid and sodium hydroxide to adjust the pH to about 3.2; and
(iv) water q.s. ad 100%.

The solutions (a) are sterilized using art-known techniques.

The neuroprotectant solution (a) of the present product is conveniently used in the treatment of patients suffering from acute hypoxia. In general it is contemplated that

an effective treatment for acute hypoxia involves administering to the patient by infusion an amount of lubeluzole N-oxide in the range of 10 to 30 ml of solution (a) or from 5 to 15 mg of the active ingredient during the first hour of therapy. During the following 24 hours about 4/3 or 133% of that amount may be administered. That is, one starts with a relatively high initial flow which is then lowered considerably. The maintenance dose may be administered for several consecutive days.

Preferably about 15 ml of solution or about 7.5 mg of the active ingredient is administered by infusion during the first hour of therapy, followed by about 20 ml of solution or about 10 mg of active ingredient during the next 24 hours. It is evident that said effective amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compound of the instant invention. The effective amount ranges mentioned hereinabove are therefore guidelines only and are not intended to limit the scope or use of the invention to any extent.

The lubeluzole N-oxide solutions may conveniently be co-administered with a physiological salt solution following to art-known infusion procedures. They may also be accompanied by administration of other anti-hypoxic drugs such as NMDA receptor antagonists, e.g. aptiganel, eliprodil, selfotel, tirilazad or remacemide; antithrombolytics, e.g. tPA, streptokinase, staphylokinase, heparin or similar agents.

Since the product is meant to be administered urgently to patients suffering from hypoxia, for example in the ambulance, emergency room or intense care unit, an infusion device or pack for the treatment of hypoxia comprising the product together with a disposable, independent drive unit is considered to be a most useful presentation of the product according to the present invention. As independent drive units for powering syringes, in particular prefilled syringes, there may be named both gas-operated and vacuum-operated drive. An interesting gas-operated intradermal drug delivery device permitting delivery of a drug at a slow rate which can be precisely controlled is described in WO-95/13838, corresponding to US-5,527,288. The device comprises a housing with one or more drug reservoirs and a single hollow needle projecting outwards for a sufficient distance so as to penetrate through the stratum corneum and epidermis into the dermis when the housing is pressed against the skin. The device can be of modular design consisting of disposable cartridge units comprising the depletable components (active ingredient, power source) and a reusable drive unit comprising amongst others the housing and the electronic controls.

The present invention evidently also concerns the use of a product as described hereinbefore for the preparation of a medicament for acute hypoxia treatment. Similarly, the present invention relates to a method of treating patients suffering from hypoxia, comprising administering to said patients a pharmaceutically effective amount of an N-oxide product as described hereinbefore.

Experimental part

Example 1 : Preparation of (-)-[cis] lubeluzole N-oxide hemihydrate.

To a stirred solution of lubeluzole (11.6 g ; 27 mmol) in dichloromethane (700 ml), cooled to -10°C, was added m-chloroperbenzoic acid (6.7 g ; 31 mmol). The reaction mixture was stirred for 24 hours, and then washed with an aqueous ammonia solution (2% ; 3 times) and water (3 times). The organis phase was dried on $MgSO_4$, filtered and evaporated, yielding 9.6 of raw material. The product (-)-[cis] lubeluzole N-oxide hemihydrate was purified by recrystallization from methylisopropylketone (mp. 182.8°C) (yield : 4.7 g ; 38.7%) $[\alpha]_D^{20}$ = -8.73° (1% in methanol) (comp. 1).

Example 2 : Pharmacological example

The useful anti-hypoxic properties of the product of the present invention can be demonstrated in the following test procedure.

Post-Treatment in a Rat Photochemical Stroke Model.

Male Wistar rats, weighing 260-280 g, were anesthetized with halothane in a N_2O/O_2 mixture. The animals were placed in a stereotactic apparatus, the scalp was incised for exposure of the skull surface, and a catheter was inserted into a lateral tail vein. Rose Bengal (30mg/kg; 15 mg/ml in 0.9% NaCl) was infused intravenously for 2 minutes in animals with normal hemodynamics and blood gases. Thereafter, the skull was focally illuminated with cold white light for 5 minutes by means of a fiber-optic bundle inside a 1-mm diameter objective. The light was aimed at the hindlimb area of the right parietal sensorimotor neocortex. Five minutes after infarct induction (i.e. 5 min after light offset), the rats are injected with either lubeluzole or lubeluzole N-oxide (comp.1). Neurologic tests, involving limb placing reactions, were conducted on the first two days after infarction at 24-hour intervals after its induction. Tactile forward and sideways placing were tested by lightly contacting the table edge with the dorsal or lateral aspect of a paw (2 tests). Proprioceptive forward and sideways placing involved pushing the paw against the table edge in order to stimulate limb muscles and joints (2 tests). Rats were also put along the edge of an elevated platform in order to assess

proprioceptive adduction : a paw was gently pulled down and away from the platform edge, and, upon sudden release, it was checked for retrieval and placing (1 test).

For each of the 5 tests, placing scores are : 0, no placing; 1, incomplete and/or delayed placing; or 2, immediate, complete placing. For each limb, the summed tactile/proprioceptive placing score, including the platform test, is maximally 10. Results are reported from the deficient hindlimb contralateral to the neocortical infarct. Six rats are used for each dose.

compound	placing score (median)	minimum	maximum
lubeluzole	7.5	6	10
lubeluzole N-oxide	9.5	8	10

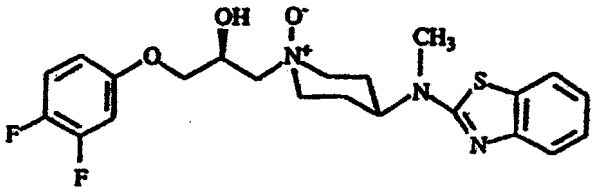
From these results one can conclude that the test animals receiving the lubeluzole N-oxide recover better from the induced stroke than those receiving lubeluzole itself.

Claims

1. An N-oxide form of lubeluzole, a pharmaceutically acceptable acid addition salt form, a solvate or a stereochemically isomeric form thereof.

2. An N-oxide according to claim 1 wherein the piperidine nitrogen is oxidized.

3. An N-oxide according to claim 2 wherein the cis and trans forms are represented by the formulae :



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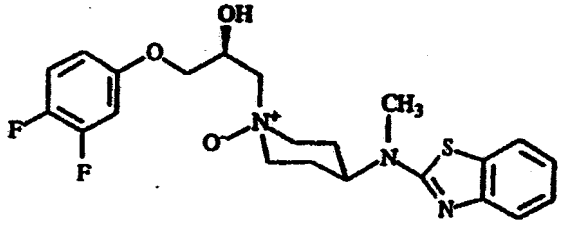

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4. An N-oxide according to claim 1 wherein the compound is (-)-[cis] lubeluzole N-oxide hemihydrate.

5. A process of preparing an N-oxide of lubeluzole comprising the steps of dissolving lubeluzole in a solvent and adding thereto a sufficient amount of a suitable oxidant.

6. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound as claimed in any one of claims 1 to 4 and a pharmaceutically acceptable carrier.

7. A composition according to claim 6 adapted for oral or parenteral administration.

8. A composition according to claim 7 wherein the N-oxide is formulated in an aqueous solution comprising water ; an isotonizing agent ; and acid, base or buffer substances sufficient to adjust the pH of the solution in the fange of from 2.5 to 3.6.

9. A composition according to claim 8 wherein the neuroprotectant solution (a) comprises :
   (i) 0.005 to 5% lubeluzole N-oxide or a pharmaceutically acceptable addition salt or a solvate thereof;
   (ii) 1 to 10% isotonizing agent;
   (iii) acid and/or base substances to adjust the pH in the range from 2.5 to 3.6 ; an
   (iv) water q.s. ad 100%.

10. A composition according to claim 8 wherein the neuroprotectant solution (a) comprises :
   (i) 0.01 to 1% lubeluzole N-oxide or a pharmaceutically acceptable addition salt or a solvate thereof;
   (ii) 2 to 10% glucose;
   (iii) hydrochloric acid and sodium hydroxide to adjust the pH in the range from 3.0 to 3.4 ; and
   (iv) water q.s. ad 100%.

11. A composition according to claim 8 wherein the neuroprotectant solution (a) comprises :
   (i) 0.05 % (w/v) lubeluzole N-oxide or a pharmaceutically acceptable acid addition salt or a solvate thereof ;
   (ii) 5 % (w/v) glucose ;
   (iii) hydrochloric acid and sodium hydroxide to adjust the pH to about 3.2 ; and
   (iv) water q.s. ad 100 %.

12. A composition according to claim 8 wherein the neuroprotectant solution (a) is present in an amount of from 10 to 30 ml, and comprises about 5 to 15 mg lubeluzole N-oxide.

13. A composition according to claim 8 wherein the neuroprotectant solution (a) is present in an amount of about 15 ml, and comprises about 7.5 mg lubeluzole N-oxide.

14. A composition according to claim 8 wherein the neuroprotectant solution (a) is present in an amount of about 20 ml, and comprises about 10 mg lubeluzole N-oxide.

15. An infusion device or pack for the treatment of stroke comprising an N-oxide product according to any one of claims 1 to 4, with a disposable, independent drive unit.

16. An infusion pack according to claim 15 wherein the independent drive unit is gas-operated or vacuum-operated.

17. A product as claimed in any one of claims 1 to 4 for use as a medicine.

18. A product as claimed in claim 17 for use in the treatment of conditions involving cerebral hypoxia.

19. A product as claimed in claim 17 for use in the treatment of stroke and head trauma.

20. A product as claimed in claim 17 for use in the treatment of ischaemic stroke, intracerebral haemorrhage and subarachnoidal haemorrhage..

INTERNATIONAL SEARCH REPORT

Interr. al Application No
PCT/EP 96/04608

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/12 A61K31/445 A61M5/142

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 501 552 A (JANSSEN PHARMACEUTICA NV) 2 September 1992 cited in the application see claims	1-7
Y	GB 2 078 729 A (BRISTOL MYERS CO) 13 January 1982 see the whole document	1-7
A	EP 0 184 257 A (JANSSEN PHARMACEUTICA NV) 11 June 1986	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 January 1997	24. 01. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inter nal Application No
PCT/EP 96/04608

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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